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Abstract

In eukaryotes, cellular and systemic metabolism is primarily controlled by mitochondrial activity. The peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) is a major regulator of mitochondrial biogenesis and function. Furthermore, PGC-1α controls many of the phenotypic adaptations of oxidative tissues to external and internal perturbations. In contrast, dysregulated metabolic plasticity is involved in the etiology of numerous diseases. Accordingly, modulation of PGC-1α levels and activity has recently been proposed as a therapeutic option for several pathologies. However, pharmacological interventions aimed at PGC-1α have to overcome inherent limitations of targeting a coactivator protein. This review focuses on the recent breakthroughs in the identification of physiological and pathophysiological contexts involving PGC-1α. In addition, perspectives regarding the therapeutic importance of PGC-1α-controlled cellular and systemic metabolism are outlined.

Introduction

Transcriptional changes in gene expression underlie the coordinated regulation of biological programs. These changes are initiated and maintained by the binding of regulatory protein complexes to DNA elements in the enhancer and promoter regions of target genes. Traditionally, DNA-binding transcription factors were thought to be the main regulators of gene expression. However, in recent years, the importance of transcriptional coregulators in the coordination of the expression of genetic programs has been appreciated [1, 2]. The family of peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1) genes illustrates how coactivators respond to environmental cues and subsequently regulate biological processes in a tissue-specific and highly coordinated manner [3-5]. All three members of this small gene family, PGC-1α, PGC-1β and PGC-related coactivator (PRC) are strong promoters of mitochondrial biogenesis and oxidative metabolism [6-8]. In contrast to PRC that is ubiquitously expressed, PGC-1α and PGC-1β are primarily found in oxidative tissues, including brain, heart, kidney, muscle, liver, brown adipose tissue (BAT) and pancreas. In these organs, PGC-1α and PGC-1β have overlapping as well as clearly distinct functions [9]. Moreover, these two coactivators are differently regulated in development and in response to nutritional and other challenges [8, 10]. However, whereas our understanding of the physiological role of PGC-1β remains rudimentary, significant progress in the study of PGC-1α has been made since its discovery more than a decade ago [11]. This review aims at

summarizing recent findings and at highlighting the potential therapeutic applications of PGC-1α.

PGC-1α regulates tissue-specific gene expression in health and disease

The PGC-1α protein is very versatile and coactivates many transcription factors [3-5]. Binding to different partners enables PGC-1α to regulate distinct biological programs. For example, a combination of coactivation events among PGC-1α, the hepatic nuclear factor 4α (HNF4α) and the forkhead transcription factor Foxo1 determines the rate of fasting-induced hepatic gluconeogenesis [12, 13]. In skeletal muscle, myofibrillar genes are controlled by PGC-1α-mediated coactivation of myocyte enhancer factor 2 (MEF2) proteins [14]. In most tissues, abnormal regulation of PGC-1α expression and protein activity results in pathological consequences. Furthermore, single nucleotide polymorphisms (SNP) of *PPARGC1A*, the PGC-1α gene, have been associated with a diverse set of human diseases (http://www.geneticassociationdb.nih.gov). PGC-1α SNPs are found throughout the protein coding region as well as in the promoter, introns and the 3' untranslated region (3' UTR). The functional consequences of the SNPs are not clearly understood and disease-association of individual SNPs seems highly population- and context-dependent.

Adipose tissue

In BAT, PGC-1α expression is regulated by cold exposure and β-adrenoreceptor agonists [11]. Subsequently, PGC-1α coactivates PPARγ and the thyroid hormone receptor (TR) on the uncoupling protein 1 (UCP-1), type 2 deiodinase (DIO2) and other BAT-specific gene promoters [11]. BAT vs. white adipose tissue (WAT) selectivity of gene expression is controlled by the distinct assembly of PGC-1α / PR(PRD1-BF1-RIZ1 homologous)-domain-containing protein (Prdm16) / C-terminal binding protein-1 (CtBP1) protein complexes in these two tissues [15]. PGC-1α function is essential for BAT-mediated adaptive thermogenesis *in vitro* and *in vivo* [9, 16, 17]. Thus, when exposed to cold, PGC-1α knockout mice rapidly become hypothermic and die after prolonged exposure [16, 17].

Levels of PGC-1α in WAT are much lower than those in BAT and the physiological role of PGC-1α in this tissue is unclear [11]. PGC-1α expression is further reduced in the subcutaneous fat of morbidly obese and of insulin resistant patients, respectively [18, 19]. In contrast, thiazoledinedione treatment and hyperleptinemia elevate PGC-1α transcription in WAT; this induction mediates some of the beneficial effects of this class of anti-diabetic drugs and of leptin, respectively [20, 21]. Ectopic expression of PGC-1α in a WAT context results in the induction of BAT-specific genes such as UCP-1 and an increase in mitochondrial activity [11, 22].

Therapeutic potential: Augmenting the function of the remaining BAT in adult humans or pushing WAT towards BAT-specific gene expression by elevating

PGC-1α could tilt energy balance towards expenditure and thereby reduce obesity (Fig. 1). Proof-of-concept for a therapeutic effect of augmented BAT content is provided by chronic β3-adrenoreceptor stimulation resulting in a lean and healthy phenotype in animal models [23]. However, it remains to be tested whether the limited capacity of PGC-1α to increase BAT gene expression in WAT is sufficient or if other factors such as Prdm16 are required to achieve a therapeutic effect [24].

Liver

The first peak of PGC-1α gene expression is observed in the liver at birth [10]. In the adult, fasting and glucagon are the main drivers of hepatic PGC-1α transcription [12, 25]. PGC-1α regulates most of the metabolic changes that occur during the transition of a fed to a fasted liver, including gluconeogenesis, fatty acid β-oxidation, ketogenesis and heme biosynthesis [12, 13, 26, 27]. Studies with knockout animals and adenovirally delivered shRNA constructs revealed a blunted hepatic fasting response in the absence of adequate levels of PGC-1α [17, 27, 28]. Accordingly, these mice develop a fasting hypoglycemia and hepatic steatosis [17, 28].

Therapeutic potential: An increase in PGC-1α levels in the liver might obviously alleviate hypoglycemia and hepatic steatosis. However, in contrast to the induction sought after in most other tissues, a repression of PGC-1α activity

holds more promise for therapy in the liver. First, hepatic PGC-1α expression is elevated in mouse models for type 1 and type 2 diabetes and probably contributes to the unchecked glucose production and hyperglycemia in diabetes [12]. Normalization of PGC-1α levels might thus help to control hepatic gluconeogenesis in these patients. Individuals with acute hepatic porphyrias, diseases caused by mutations in the heme biosynthetic pathway, often suffer from fasting-induced acute attacks that can be alleviated by glucose and heme administration [29]. PGC-1α has been identified as one of the main culprits in the precipitation of acute porphyric attacks in fasting [27]. These attacks might be prevented by pharmacological interventions that thwart the induction or activity of PGC-1α [29, 30]. Furthermore, PGC-1α regulates the genes encoding homocysteine synthesis enzymes in the fasted liver [31]. High plasma homocysteine is an independent risk factor for the development of cardiovascular diseases. Accordingly, inhibition of PGC-1α could result in a drop of plasma homocysteine levels and thereby a reduction of the risk for cardiovascular diseases [31]. Finally, the hepatitis B virus (HBV) uses the transcriptional machinery that regulates the hepatic fasting response for amplification [32]. Accordingly, HBV gene expression and life cycle, and thus the viral-host interaction, are under the control of PGC-1α [32]. Repression of PGC-1α activity might present a new anti-viral therapy for hepatitis B and help to restrict the viral load in this disease.

Brain

In the developing brain, PGC-1α transcription peaks two weeks postnatally in many regions, a period of significant metabolic changes, mitochondrial biogenesis and synaptic remodeling [33]. The highest PGC-1α concentrations are found in γ-aminobutyric acid (GABA)-positive neurons in the cortex, hippocampus and cerebellum [33]. One of the existing global PGC-1α knockout line exhibits increased anxiety [17], whereas a second model shows a profound hyperactivity [16]. Other behavioral changes include hind limb clasping, dystonic posturing, an exaggerated startling response and stimulus-induced myoclonus [16]. Besides the behavioral abnormalities, spongiform-like vacuolization events are observed in the dorsolateral striatum [16], the vicinity of pyramidal neurons [17], and more sporadically, in other regions of the brain of PGC-1α knockout mice [16]. Furthermore, the substantia nigra and the CA1 neurons of the hippocampus are more susceptible to degenerative events triggered by the reactive oxygen species (ROS)-generating 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and kainic acid, respectively, in these animals [34]. These findings suggest an important involvement of PGC-1α in neuronal maintenance and function.

Therapeutic potential: Mitochondrial dysfunction and oxidative stress are associated with many neurodegenerative disorders, including Parkinson's, Alzheimer's, Huntington's, Friedreich's ataxia and amyotrophic lateral disorder (ALS) [35, 36]. PGC-1α coordinately regulates the entire mitochondrial program

concomitant with an increase in the ROS detoxification system [34]. Reduced PGC-1α expression in Huntington's patients, the association of PGC-1α SNPs with the age of onset of Huntington's [37] and the Huntington's-like phenotype in PGC-1α knockout suggest that PGC-1α is crucial for the maintenance of proper striatal function [16, 38, 39]. A normalization of PGC-1α expression in the striatum of Huntington's patients might thus constitute a promising therapeutic option [40-42]. In addition, the wide-spread neuronal lesions and the susceptibility to chemically-induced neurodegeneration in different regions of the brain of PGC-1α knockout animals imply that PGC-1α has a broader role in neuroprotection beyond that related to Huntington's disease [16, 34].

Skeletal muscle

In the contracting muscle fiber, the main signaling pathways converge on PGC-1α to increase expression levels and the activity of this coactivator [3, 43, 44]. For example, p38 mitogen-activated protein kinase (p38 MAPK) and AMP-dependent kinase (AMPK) are rapidly activated in exercise and subsequently phosphorylate the PGC-1α protein. In addition, PGC-1α transcription is regulated by the motor neuron-induced rise in intracellular calcium, AMPK, β2-adrenoreceptor signaling, nitric oxide and thyroid hormone [5]. As a consequence, PGC-1α levels in skeletal muscle are elevated following bouts of endurance exercise. PGC-1α is primarily found in type I and IIa slow-twitch, high endurance muscle fibers and regulates the adaptations to exercise [14]. In fact,

ectopic expression of PGC-1α in skeletal muscle is sufficient to promote a fiber-type switching towards oxidative muscle fibers and bestow a trained phenotype onto mice [14, 45].

Abnormally low PGC-1α levels have been described in skeletal muscle of type 2 diabetic patients and physically inactive individuals [46, 47]. Mice with reduced or ablated PGC-1α gene expression suffer from a decreased exercise capacity, abnormal systemic glucose and insulin homeostases, systemic inflammation and activity-dependent fiber damage [48, 49]. Paradoxically, transgenic mice with elevated PGC-1α levels in muscle are prone to develop peripheral insulin resistance on a high fat-containing diet [50].

Therapeutic potential: Many diseases are associated with inactive skeletal muscle [51]. In animal models, transgenic elevation of PGC-1α in muscle blunts inactivity-induced fiber atrophy [52], reduces muscle wasting triggered by the statin class of drugs [53], ameliorates Duchenne muscular dystrophy [54] and a specific form of mitochondrial myopathy [55]. Since PGC-1α promotes an exercised phenotype in muscle, the therapeutic potential of PGC-1α against diseases that are associated with dysregulated muscle function is extremely broad.

PGC-1α controls the transcription of several genes encoding oxidative phosphorylation (OXPHOS) genes that are dysregulated in muscle of type 2

diabetic patients [46, 47]. The specific disruption of the interaction between PGC-1α and the estrogen-related receptor α (ERRα) using an inverse agonist in muscle cells in culture promotes a change in gene expression similar to that observed in muscle of diabetic patients [56]. Activation of the PGC-1α/ERRα axis could thus be a novel therapeutic approach against insulin resistance and type 2 diabetes [57]. However, the data from gain- and loss-of-function animal models of PGC-1α in muscle imply a complicated relationship between the expression of this coactivator and systemic glucose and insulin levels that has yet to be clarified [49, 50].

Heart

In the heart, PGC-1α transcription is induced at birth and correlates with metabolic maturation and remodeling [58]. As in other tissues, cardiac PGC-1α strongly promotes mitochondrial function and fatty acid β-oxidation [59]. In several mouse models for heart disease accompanied with a substrate switch from fatty acid to glucose utilization, expression of PGC-1α is reduced [60]. At baseline, heart function of PGC-1α knockout mice appears normal [17, 61]. However, the cardiac reserve under stress conditions is impaired in mice with an ablated PGC-1α gene [61] and accordingly, these mice have a diminished cardiac capacity in exercise [17]. In addition, prolonged pressure overload by transverse aortic constriction precipitates ventricular dysfunction and clinical signs of heart failure in PGC-1α knockout animals [62]. Interestingly, ectopic

expression of PGC-1α in the heart at superphysiological levels also results in cardiomyopathy and heart failure in mice [58].

Therapeutic potential: Moderate elevation or normalization of PGC-1α expression in the failing heart might be sufficient to switch substrate usage from glucose back to fatty acids and restore adequate energy production [62]. Thereby, PGC-1α could be cardioprotective against certain insults [60]. In contrast, insulin-resistant hearts rely heavily on fatty acid oxidation and there, PGC-1α levels are elevated [63]. It is unclear if upregulation of cardiac PGC-1α in insulin resistance is an adaptive or a maladaptive process. In the former case, a reduction of PGC-1α expression should be the therapeutic goal. However, if the increase of PGC-1α is an adaptive process to cope with the excess amount of fatty acids, a further elevation might be therapeutically beneficial [3, 60].

Pancreas

In obese mice, insulin resistant animal models and in a partial pancreatectomy as a model for β cell decompensation, the transcriptional rate of the PGC-1α gene in the pancreas is increased over the normally low basal levels [64]. In pancreatic islets, PGC-1α prevents membrane polarization and induces glucose-6-phosphatase and thereby reduces insulin secretion [64]. Notably, a second study of PGC-1α in human pancreatic islets resulted in opposite findings [65]. A common PGC-1α SNP was associated with reduced PGC-1α expression and

insulin secretion in islets of tissue donors [65]. In addition, silencing of PGC-1α gene expression in isolated human islets likewise led to impaired insulin secretion [65].

Therapeutic potential: At the moment, the diametrically opposed results of these two studies are difficult to accommodate. Until these issues are resolved, it is unclear whether a suppression or an induction of PGC-1α activity in pancreatic islets is the more promising avenue to restore insulin secretion in type 1 and type 2 diabetes.

Bone and cartilage

Parathyroid hormone-induced cAMP signaling is a major pathway in osteoclast activation [66]. PGC-1α is a primary target gene of this signaling cascade and synergistically with Nurr1, a cAMP-induced orphan nuclear receptor, increases the transcription of osteopontin and osteocalcin, two key genes in bone formation [66]. Given the significant role of ERRα, one of the strongest interaction partners of PGC-1α, in osteoblasts and osteoclasts [67] and the coactivation of the vitamin D receptor by PGC-1α [68], an important function for PGC-1α in osteogenesis seems likely. These findings are intriguing in regard to a report showing a role of PGC-1α in chondrogenesis [69] suggesting an even broader implication for PGC-1α in the developing skeleton.

Therapeutic options: An activation of PGC-1α might be useful in osteoporosis or other disease associated with reduced bone density and morphology [66]. Similarly, PGC-1α could be a promising target for molecular engineering of cartilage in the clinical setting, e.g., osteoarthritis and other chondrodystrophies [69].

Problems, pitfalls and opportunities

As a transcriptional coactivator, PGC-1α lacks functional DNA- and ligand-binding domains and therefore is not amenable to direct pharmacological intervention. Strategies to alter the availability of PGC-1α thus have to aim at transcriptional regulation of the gene, modifications of the protein or the interaction with binding partners. Modulation of PGC-1α transcription is hampered by the tight regulation of cellular metabolism. Accordingly, despite different screening efforts [70, 71], clinically interesting compounds that persistently induce PGC-1α transcription are elusive. Optimally, such drugs would act in a tissue-specific manner to circumvent unwanted side-effects by elevating PGC-1α in non-target tissues. For example, an elevation of PGC-1a in WAT by thiazoledinedione drugs has been reported [20]; however, it is unclear whether this induction is direct, secondary to other events or even sufficient to contribute to the therapeutic effect of this class of drugs.

Posttranslational modifications of the PGC-1α protein alter the half-life and the specificity towards binding partners (Fig. 2). For example, PGC-1α is phosphorylated by AMPK at two different sites [44]. Metformin, a clinically used anti-diabetic drug mediates at least some of its therapeutic effect through activation of AMPK. Furthermore, deacetylation of 13 lysine residues on PGC-1α by the mammalian silencing information regulator 2-ortholog SIRT1 increases PGC-1α activity and thereby targets gene expression in muscle and liver [72, 73]. Resveratrol and other, more specific SIRT1 activators are promising drugs against aging and aging-related diseases acting partially through PGC-1α [74]. Other known modifications of PGC-1α include phosphorylations by p38 MAPK [75, 76] and Akt2/protein kinase B [77], methylation by protein arginine methyltransferase 1 (PRMT1) [78], ubiquitination [79] and O-linked β-N-acetylglucosamination [80]. Proteins with such enzymatic activities are attractive drug targets for which specific activators and inhibitors can be designed. Following the posttranslational modifications that modify the specificity of PGC-1α, the transcription of selective groups of target genes is altered (Fig. 2). Thus, pharmacological manipulation of these enzymes upstream of PGC-1α might result in a fine-tuned modulation of PGC-1α activity in a tissue- and target gene-specific manner [5].

PGC-1α regulates biological programs by interacting with different transcriptional complexes. For instance, the strong potentiation of the transcriptional activity of ERRα by PGC-1α is responsible for mitochondrial OXPHOS gene expression in

muscle and other tissues and a specific disruption of this interaction selectively reduces the expression of these, but not other PGC-1α target genes [56]. The use of partial agonists for ligand-binding transcription factors that modulate the binding of individual coactivators [81] or of compounds that selectively disrupt or enhance protein-protein interactions [56] could thus be another approach for a specific modulation of PGC-1α activity. Furthermore, pharmacological interventions targeting the assembly of the PGC-1α–containing transcriptional complex that includes the p160 myb-binding protein [82], histone acetyl-transferase enzymes (HAT) [83], members of the TRAP/DRIP/mediator complex [84] and other proteins [85] are alternative strategies with therapeutic potential.

Finally, indiscriminate changes in the level of PGC-1α in either direction are most likely equally detrimental (Fig. 3). For example, cardiomyopathy and heart failure develop with sub- and superphysiological levels of PGC-1α [58, 62]. In skeletal muscle, an increased exercise capacity was observed in a mouse line with moderate transgenic expression of PGC-1α [14]. However, the roughly ten-fold increase in PGC-1α transcript levels in these animals might already be excessive for normal insulin sensitivity [50]. In contrast, an even more modest elevation of PGC-1α as demonstrated in an *in vivo* transfection experiment clearly increased insulin sensitivity in skeletal muscle [86]. Higher expressing mouse lines suffer from displacement of the contractile apparatus by excess mitochondria, weight loss, fiber atrophy and muscle wasting [14, 87], reminiscent of the fiber damage of muscle-specific knockout animals [48, 49]. Modulation of PGC-1α thus has to

aim at either a moderate alteration or a normalization of PGC-1α activity within a therapeutically beneficial window that might be tissue- and context-dependent.

Perspectives

The transcriptional coactivator PGC-1α plays a key role in maintaining cellular metabolism. Dysregulation of gene expression and gene polymorphisms of PGC-1α have accordingly been found in a wide variety of different pathological contexts. Furthermore, therapeutic efficacy of PGC-1α modulation has been demonstrated in animal models for different diseases. Thus, pharmacological regulation of PGC-1α expression and activity might be a promising novel approach for the prevention and therapy of a number of pathologies despite the inherent difficulties of targeting a coactivator. On the other hand, coactivators exhibit some features that could be exploited for clinical use. By coordinating different steps in biological programs through the integration of the activity of many transcription factors, coactivators have kinetic advantages in controlling biological programs over transcription factor-mediated regulation [1]. Furthermore, combinatorial combinations of posttranslational modifications of coregulators exponentially increase the degree of specification of these proteins [2, 5]. Thus, a selective targeting of PGC-1α could potentially result in a fine-tuned and highly specific response, which is unattainable by modulation of transcription factors. Finally, modulation of PGC-1α in one tissue might trigger distal effects in other organs. For example, observations from muscle-specific

loss-of-function mouse lines suggest that PGC-1α links muscle function to systemic inflammation and ultimately, the risk of developing many chronic diseases [48, 49, 51]. If these findings are substantiated, then modulation of PGC-1α might have a much broader therapeutic applicability [51]. Obviously, big gaps of knowledge about the function of PGC-1α, and even more about PGC-1β and PRC exist. Hopefully, a more comprehensive understanding of the therapeutic potential of the PGC-1 family of coactivators will emerge from future studies addressing mechanistic and physiological aspects of these intriguing proteins.

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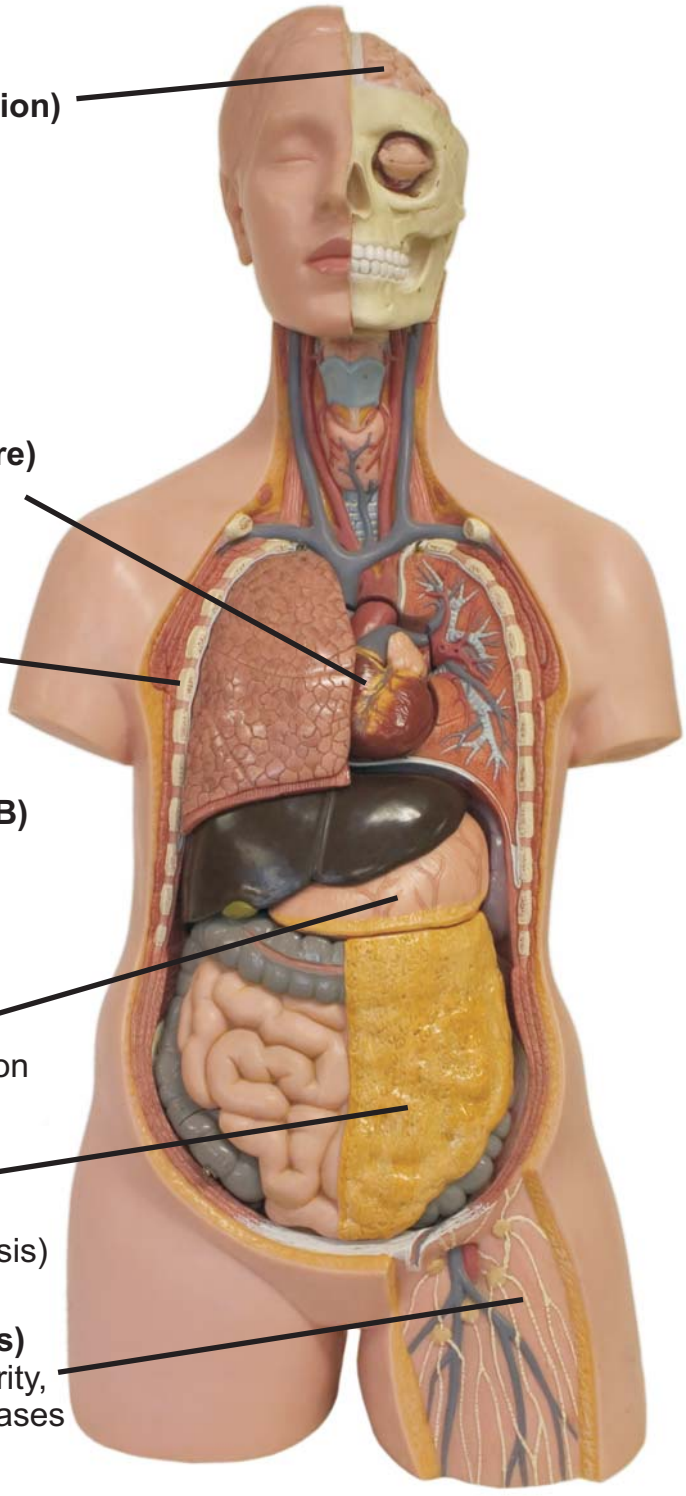
Figure Legends

Fig. 1. Therapeutic potential of PGC-1α. For a number of tissues, different functions of PGC-1α have been described. A modulation of PGC-1α expression and activity could have therapeutic implications in the diseases listed for each of these organs. Abbreviations: BAT, brown adipose tissue; CVD, cardiovascular diseases.

Fig. 2. Posttranslational modifications alter the specificity of PGC-1α. The specificity of PGC-1α to interact with its binding partners is altered by posttranslational modifications of the PGC-1α protein. For example, phosphorylation of PGC-1α by the AMP-dependent kinase (AMPK) primarily affects PGC-1α target genes that are involved in cellular metabolism. Selective activation of neuromuscular junction (NMJ) genes in synaptic nuclei of the muscle fiber is achieved by different phosphorylations of PGC-1α through motor neuron-derived signals. Abbreviations: OXPHOS, oxidative phosphorylation.

Fig. 3. Clinical modulation of PGC-1α has to occur in a therapeutically beneficial window. Super- and subphysiological expression of PGC-1α cause detrimental effects as described for heart and skeletal muscle. A pharmacological modulation should thus aim at a moderate increase or a normalization of pathologically dysregulated PGC-1α. The therapeutic window might differ between tissues and contexts.

Fig. 1



Brain (neurodegeneration)
neuronal integrity

Heart (cardiomyopathy, heart failure)
heart rate and contractile function

Skeleton (osteoporosis, arthritis)
bone and cartilage formation

Liver (diabetes, porphyria, CVD, hepatitis B)
fasting-induced gluconeogenesis, heme biosynthesis, homocysteine synthesis and hepatitis B viral replication

Pancreas (diabetes)
modulation of insulin secretion

Fat (obesity)
BAT-like phenotype (fatty acid mobilization, reduction of fat pads, increase in thermogenesis)

Muscle (muscle atrophy, dystrophies, diabetes)
endurance capacity, fiber size, function and integrity, capillarisation, lipid, insulin and glucose homeostases

Fig. 2

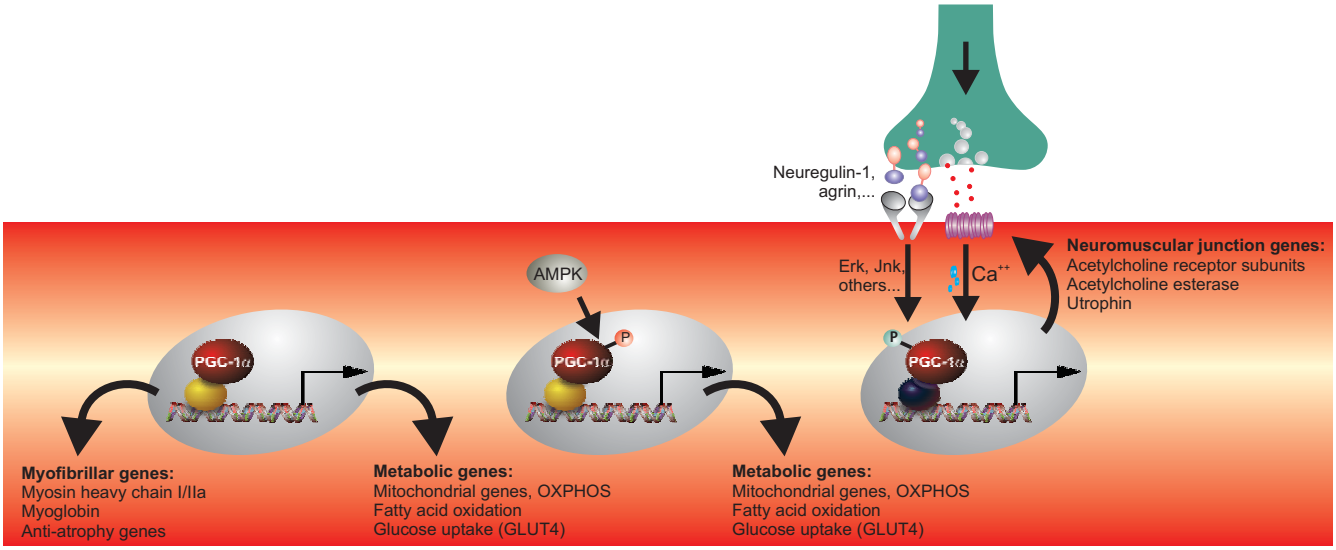
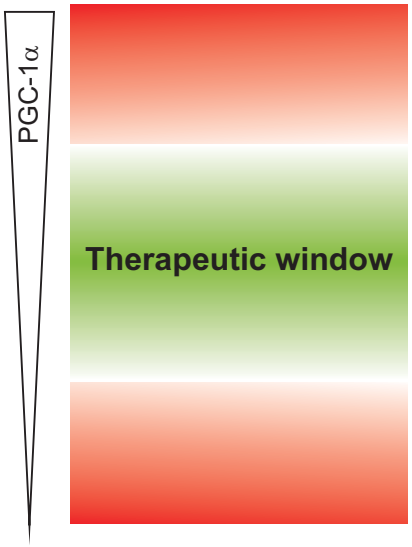

Neuregulin-1,
agrin,...
Erk, Jnk,
others...
Ca++
Neuromuscular junction genes:
Acetylcholine receptor subunits
Acetylcholine esterase
Utrophin
AMPK
P
PGC-1α
Myofibrillar genes:
Myosin heavy chain I/IIa
Myoglobin
Anti-atrophy genes
Metabolic genes:
Mitochondrial genes, OXPHOS
Fatty acid oxidation
Glucose uptake (GLUT4)
Metabolic genes:
Mitochondrial genes, OXPHOS
Fatty acid oxidation
Glucose uptake (GLUT4)

Fig. 3



	Heart	Muscle
	Cardiomyopathy Heart failure	Fiber damage Muscle wasting Insulin resistance
Therapeutic window	Cardioprotection	Increased muscle function Reduced atrophy and fiber damage Improved glucose and insulin homeostases
	Cardiomyopathy Heart failure	Reduced exercise capacity Fiber damage Systemic inflammation Dysregulated glucose and insulin homeostases